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Effect of chloride dialysate concentration on metabolic acidosis in maintenance hemodialysis patients

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Abstract

Hyperchloremia is one of the multiple etiologies of metabolic acidosis in hemodialysis (HD) patients. The aim of the present study was to determine the influence of chloride dialysate on metabolic acidosis control in this population. We enrolled 30 patients in maintenance HD program with a standard base excess (SBE) ≤2 mEq/L and urine output of less than 100 mL/24 h. The patients underwent dialysis three times per week with a chloride dialysate concentration of 111 mEq/L for 4 weeks, and thereafter with a chloride dialysate concentration of 107 mEq/L for the next 4 weeks. Arterial blood was drawn immediately before the second dialysis session of the week at the end of each phase, and the Stewart physicochemical approach was applied. The strong ion gap (SIG) decreased (from 7.5 ± 2.0 to 6.2 ± 1.9 mEq/L, P = 0.006) and the standard base excess (SBE) increased after the use of 107 mEq/L chloride dialysate (from -6.64 ± 1.7 to -4.73 ± 1.9 mEq/L, P < 0.0001). ΔSBE was inversely correlated with ΔSIG during the phases of the study (Pearson r = -0.684, P < 0.0001) and there was no correlation with Δchloride. When we applied the Stewart model, we demonstrated that the lower concentration of chloride dialysate interfered with the control of metabolic acidosis in HD patients, surprisingly, through the effect on unmeasured anions.

Key words: Chloride dialysate; Hemodialysis; Metabolic acidosis; Stewart model

Introduction

Metabolic acidosis is a common feature of chronic kidney disease (CKD), worsening progressively with renal function decline (1). Nearly one-third to one-half of patients on maintenance hemodialysis (HD) have a predialysis serum bicarbonate level below 22 mEq/L, in contrast to a serum level at or above 22 mEq/L as suggested by the K/DOQI statement guidelines (2). In these patients, metabolic acidosis has detrimental effects such as renal osteodystrophy, inflammation and impaired nutritional status (3-7).

The real determinants of acidosis in maintenance HD patients can be reanalyzed using the Stewart model, which considers water dissociation at the center of the acid-basic status of body fluids and is based on six simultaneous equations, incorporating the Laws of Mass Action, Mass Conservation and Electrical Neutrality (8).

The human plasma is a complex solution that consists of fully dissociated ions ("strong ions" such as sodium, potassium, chloride, and lactate), partially dissociated "weak" acids (such as albumin and phosphate), and volatile buffers (carbonate species). Therefore, serum pH is determined by three independent variables: partial carbon dioxide tension (pCO_2), the difference in charge between strong cations and strong anions ("strong ion difference" or SID) in plasma, and the total plasma concentration of nonvolatile weak acid buffers, mainly albumin and inorganic phosphate, with bicarbonate being a dependent variable (8,9).

Although direct measurements on hemodialysis patients should be performed, the Stewart approach has been used to predict mortality in different populations. A better mortality prediction performance has been demonstrated using this methodology when compared to other criteria, such as base excess and anion gap, especially in populations such as

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critical pediatric and trauma patients (10,11).

Liborio et al. (12) performed a cross-sectional study to identify and quantify each component of metabolic acidosis in hemodialysis patients using the physicochemical approach. Their study showed that metabolic acidosis in this population was due to retention of unmeasured anions, hyperchloremia and hyperphosphatemia. Thus, it was proposed that hyperchloremia was an important component of metabolic acidosis in hemodialysis patients.

As the chloride ion is one of the multiple factors involved in metabolic acidosis in hemodialysis patients, we analyzed one of the main sources of this anion, i.e., the dialysis solution. The aim of the present study was to detect the effect of chloride dialysate on metabolic acidosis control, while maintaining a stable bicarbonate dialysate level in this population.

Patients and Methods

Hemodialysis patients and study design

We enrolled 30 patients submitted to a maintenance hemodialysis program three times a week for at least 4 h, within a minimum period of 3 months. The patients were selected from a single dialysis center according to the following inclusion criteria: predialysis blood gas with standard base excess (SBE) ≤2 mEq/L, urine output of less than 100 mL/24 h, 18 years of age or older; arterial pressure levels below 140/90 mmHg with or without antihypertensive therapy; interdialytic fluid gain ≤50 mL/kg, and absence of hypertensive emergency events or congestive heart failure.

The study was divided into two phases from May to July 2009. In the first phase, the chloride dialysate concentration was set at 111 mEq/L for 4 weeks and in the second phase, for the next 4 weeks, at 107 mEq/L. The setting of chloride dialysate concentration was attained by modifying sodium dialysate in the same proportion. The dialysate composition was 2.0 mEq/L potassium, 32 mEq/L bicarbonate, 3.0 mEq/L acetate, 3.5 mEq/L calcium, and 1.0 mEq/L magnesium. Sodium was 140 mEq/L during the first phase and 136 mEq/L during the second phase. The ionic concentrations of the dialysate were measured directly to identify changes in sodium and chloride levels according to the study phase.

Vascular access was achieved through a native arteriovenous fistula in all patients, without evidence of stenosis or recirculation. A high-flow and high-efficiency dialyzer was used (F-80, Fresenius, Germany). The dialysis equipment consisted of a Fresenius 4008-S instrument and the dialysate flow was set at 500 mL/min. Blood flow was set at a range of 350-450 mL/min. The Ethics Committee of Federal University of Ceará approved the study design and written informed consent was obtained from all patients.

Analysis of blood

Laboratory analysis was carried out using arterial blood drawn immediately before the midweek dialysis session during the last week of use of modified dialysate concentration. All samples were analyzed with a Cobas 400 Plus analyzer (Roche Diagnostics, Germany) and standard reagents were used to measure biochemical variables, including urea, sodium, chloride, potassium, calcium, phosphate, magnesium, and albumin. Blood gases and lactate were analyzed using Eletrodo Rapid lab 348 (Bayer, Germany). SBE was determined according to the Van Slyke equation.

Interpretation of quantitative acid-base analysis

The quantitative physicochemical analysis of the results was performed using the Stewart-Figge approach. This model involves the following principles: 1) apparent SID (SIDa) = $[Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-] - [lactate^-]$, expressing all concentrations in mEq/L; 2) effective SID (SIDe), representing the weak acid effect on the balance of electrical charges in plasma, was calculated using the formula: SIDe = $[(2.46 \times 10^{-8}) \times (pCO_2/(10^{-pH}))] + [(albumin) \times (0.123 \times pH - 0.631)] + [(phosphate) \times (0.309 \times pH - 0.469)]$, pCO_2 in mmHg, albumin in g/L, and phosphate in mM; 3) strong ion gap (SIG) = SIDa - SIDe, represents the unmeasured anions (sulfate, ketoacids, citrate, pyruvate, acetate, and others).

Adequacy of dialysis and estimated protein intake

The adequacy of dialysis was evaluated by the equilibrated Kt/V (eq Kt/V) equation, obtained from the single pool Kt/V (sp Kt/V), and estimated protein intake by the normalized protein catabolic rate: 1) sp Kt/V = -ln (Req - 0.008 x t) + [4 - (3.5 x Req)] x UF/W; where ln = natural logarithm, Req = post- and pre-dialysis blood urea nitrogen ratio, t = duration of hemodialysis session in hours, UF = ultrafiltration volume in liters, W = post-dialysis weight in kg; 2) eq Kt/V = sp Kt/V (1 - 0.60 / t) + 0.03; 3) PCRn ($g \cdot kg^{-1} \cdot day^{-1}$) = (pre-dialysis BUN / [25.8 + (1.15 / Kt/V)] + [(56.4 / Kt/V)]) + 0.168; where BUN = blood urea nitrogen (mM).

Statistical analyses

Data are reported as means ± SD. Continuous variables were compared between groups using the D'Agostino and Pearson normality test, followed by the paired *t*-test. The correlation coefficient (r) between pairs of variables was determined using Pearson's method. Values of $P < 0.05$ were considered to be statistically significant. All statistical analyses were performed using the Graph Pad Prism program, version 5.02 (Graph Pad software, USA).

Results

Demographic features

Twenty-one male and 9 female patients were studied. Mean age was 47 ± 15.7 years (Table 1). The etiology of CKD was chronic glomerulonephritis (N = 5), diabetic nephropathy (N = 3), hypertensive nephrosclerosis (N = 6), and polycystic kidney disease (N = 2). Fourteen patients had CKD of unknown etiology. The patients' mean time

on dialysis treatment was 7.6 ± 4 years. Five patients had undergone previous renal transplantation.

Acid-base variables in hemodialysis patients

After the use of a chloride dialysate of 111 mEq/L, the patients persisted with a mean SBE of -6.64 ± 1.7. Analysis based on the physicochemical approach revealed that metabolic acidosis in these patients was due almost exclusively to the accumulation of unmeasured anions, represented by a SIG of 7.5 ± 2.0 mEq/L. SIDa was within the normal range, similar to the other determinants of acid-base status.

When the chloride dialysate level was fixed at 107 mEq/L, SBE improvement was observed (from -6.64 ± 1.7 to -4.73 ± 1.9 mEq/L, P < 0.0001). As expected, serum sodium was reduced (from 138 ± 2.44 to 137 ± 2.07 mEq/L, P = 0.02), as also was serum chloride (from 104.1 ± 2.7 to 102.9 ± 2.8 mEq/L, P = 0.03). When investigating the cause of metabolic acidosis correction, we observed no difference in SIDa (see Table 2) and the increase in SBE (1.9 mEq/L) was almost completely explained by SIG reduction (1.3 mEq/L).

Influence of unmeasured anions on standard base excess

Pearson's correlation analysis was also used to investigate the interrelationship between the ΔSBE (difference between SBE after using chloride dialysate of 111 and 107 mEq/L) and Δ of each of the acid-base determinants. We observed that ΔSBE was inversely correlated with the unmeasured anion variation (ΔSIG) between the two study phases, which was the only significant variable (Pearson r = -0.684, P < 0.0001). Other variables, Δsodium, Δchloride, Δpotassium, Δcalcium, Δmagnesium, Δlactate and Δphosphate, did not correlate with SBE.

In addition to the analysis of acid-base variables, there was no statistically significant difference between components that could be involved in the control of metabolic

Table 1. Characteristics of hemodialysis patients.

Clinical characteristics	
Age (years)	47 ± 15.7
Gender (male/female)	21/9
Weight (kg)	64.25 ± 12.6
Height (m)	1.64 ± 0.1
BMI (kg/m^2)	24 ± 4.3
Mean time on hemodialysis (years)	7.6 ± 4.0
Etiology of CKD	
Unknown	14 (46.6%)
Hypertensive nephrosclerosis	6 (20%)
Chronic glomerulonephritis	5 (16.7%)
Diabetes mellitus	3 (10%)
Polycystic kidney disease	2 (6.7%)
Previous renal transplantation	5 (17%)

Data are reported as means ± SD or as number with percent in parentheses for 30 patients. BMI = body mass index; CKD = chronic kidney disease.

Table 2. Comparison of acid-base variables after the use of chloride dialysate of 111 and 107 mEq/L.

Variable	Chloride dialysate (111 mEq/L)	Chloride dialysate (107 mEq/L)
pH	7.32 ± 0.05	7.33 ± 0.04
Bicarbonate (mEq/L)	19.2 ± 1.40	20 ± 2.14*
Sodium (mEq/L)	138 ± 2.44	137 ± 2.07*
Potassium (mEq/L)	5.06 ± 0.68	4.87 ± 0.52
Calcium (mEq/L)	9.2 ± 0.65	9.1 ± 0.73
Magnesium (mg/dL)	2.66 ± 0.25	2.7 ± 0.28
Chloride (mEq/L)	104.1 ± 2.7	102.9 ± 2.8*
Lactate (mEq/L)	2.09 ± 0.50	1.95 ± 0.54
SIDa (mEq/L)	41.13 ± 1.75	41.41 ± 1.90
SIDe (mEq/L)	33.24 ± 2.9	34.59 ± 2.4*
Phosphate (mg/dL)	4.41 ± 1.6	4.65 ± 1.5
Albumin (mEq/L)	4.28 ± 0.28	4.28 ± 0.32
Unmeasured anions (SIG)	7.5 ± 2.0	6.2 ± 1.9*
pCO_2 (mmHg)	37.56 ± 3.4	38.78 ± 3.9
SBE (mEq/L)	-6.64 ± 1.7	-4.73 ± 1.9*

SIDa = apparent strong ion difference; SIDe = effective strong ion difference; SIG = strong ion gap; PCO_2 = partial carbon dioxide tension; SBE = standard base excess. *P < 0.05 compared to 111 mEq/L (paired *t*-test).

acidosis in hemodialysis patients, according to study phase, as eq Kt/V, PCRn, phosphorus binders, interdialytic weight gain, and serum osmolality.

Discussion

Although acidosis has complex and multiple etiologies in maintenance hemodialysis, the acidosis composition is still unknown (13). In addition to the unmeasured anions, hyperchloremia and phosphate are important components.

Until recently, it was difficult to demonstrate which factors affected by dialysis had the most influence on acidosis. Regardless of bicarbonate diffusion has been the center of acidosis correction, it is necessary to remove the anions resulting from metabolism, while bicarbonate is being replaced. Although the identification of which components are mainly responsible for the unmeasured anions, the physicochemical approach made their quantification possible through relatively simple equations.

While analyzing the factors involved in the maintenance of patients' metabolic acidosis, significant differences in SBE were observed. This variable is frequently used to quantify the degree of metabolic acidosis, and can be used as a tool to demonstrate changes in the components of the acid-base balance, especially in critically ill patients (14). Although it is considered obsolete by some investigators, the change in SBE is directly related to the concentration of weak acids, which is independent of the respiratory component, thus being preferred to bicarbonate (15).

Even though dialysis plays a role in the correction of acidosis, the influence of dialysate ion concentration on this acid-base control process is unexplored. In the present study, when sodium and chloride dialysate concentrations were reduced, we observed a better correction of SBE than during the use of a high sodium and chloride concentration dialysate, although the same bicarbonate concentration was used in the dialysate.

More noteworthy is the fact that metabolic acidosis correction was mainly due to a reduction of unmeasured anions, represented by SIG. At the beginning of the study, it was hypothesized that acidosis correction was more predictable by an increase in SIDa. This was possible by reducing serum chloride levels due to reduced concentration in the dialysate. At the same time, a lesser improvement in serum sodium was predictable due to individual and constant osmolar set points (16), suggesting that its variations have a minor impact on acid-base variables.

Surprisingly, metabolic acidosis improvement was observed due to unmeasured anion reduction. We suggest that the reduction in serum chloride during the post-dialysis period can facilitate redistribution from the intracellular or interstitial compartment, a shift described in septic animals by Kellum et al. (17). This decrease in intracellular chloride can improve the intracellular capacity of buffering other negative charges, reducing plasma unmeasured anions.

However, this analysis became more complex when we considered multiple cellular aqueous compartments (plasma, erythrocytes, interstitial and intracellular compartments), containing a variety of strong ions and weak acids and incorporating several interlinked Gibbs-Donnan equilibria (18). Recently, a similar pattern has been demonstrated in septic patients, in whom a higher renal clearance of chloride was not accompanied by a reduction in serum chloride, but by a reduction in unmeasured anions (19).

Another possible explanation may be found in the dialysate compartment. It has been suggested that a higher dialysate chloride concentration, through Gibbs-Donnan equilibrium across the dialyzer membrane, partially prevents an adequate clearance of unmeasured anions due to a charge effect, i.e., electric repulsion of a negative charge. Moreover, based on this principle, it is not possible to exclude that an improvement in bicarbonate diffusion might have been the result of using a lower dialysate chloride concentration.

Although a decrease in SIG is suggestive of unmeasured anion reduction, this study presents limitations: unmeasured anions are estimated based on calculations using many variables and the possibility of minor changes in each one can result in significant variations in their final value.

Additional studies may be needed to demonstrate the relationship between the effects of the prescribed dialysis and long-term effects of acidosis, accumulation of unmeasured anions, hyperchloremia and its effects on bone metabolism, inflammation and nutrition.

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